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γ-ALKYLATION OF UNSATURATED KETONES AND ESTERS: ZINC BROMIDE-CATALYSED ALKYLATION OF *O*-SILYLATED DIENOLATES[1]

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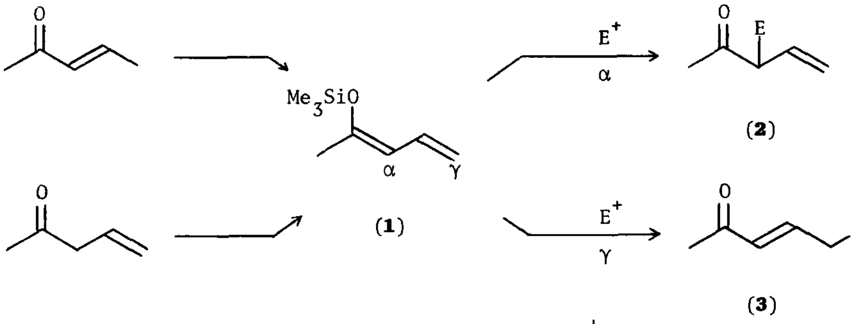
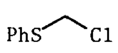
Summary: The *O*-silylated dienolates of unsaturated ketones and esters can be alkylated using zinc bromide catalysis to give predominantly the γ-alkylated carbonyl compounds. The substitution pattern of the substrate (**1**), favours, in certain cases, very high or complete γ-selectivity.

In the preceding paper we report that sulphenylation of *O*-silylated dienolates occurs with high γ-selectivity. In this paper we report on the α- versus γ-selectivity of a number of carbon electrophiles in their reactions with *O*-silylated dienolates (**1** → **2** + **3**). In almost all cases tried, the major product is that (**3**) of γ-attack, and in some cases it is overwhelmingly so. These results complement the high α-selectivity usually shown by lithium dienolates,[2,3,4] and supplement the reactions of copper dienolates with allyl halides[5] and less direct methods of encouraging γ-selectivity.[6]

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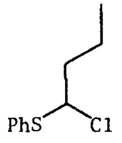
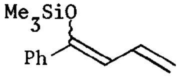
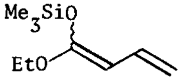
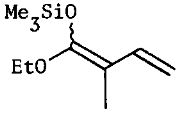
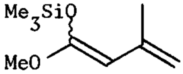
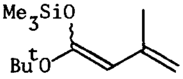
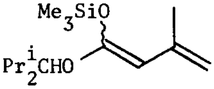
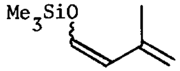
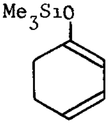

(5)

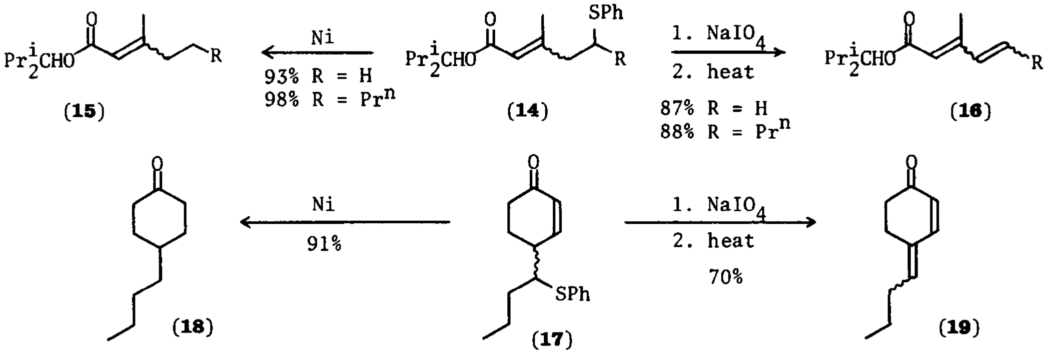
The electrophiles we have studied most thoroughly are chloromethyl phenyl sulphide (**4**) and α-chloro-n-butyl phenyl sulphide (**5**) in the presence of zinc bromide; we have already shown that these are useful alkylating and alkylidenating agents for the *O*-silylated enolates of saturated carbonyl compounds.[7] The results are summarised in the Table.

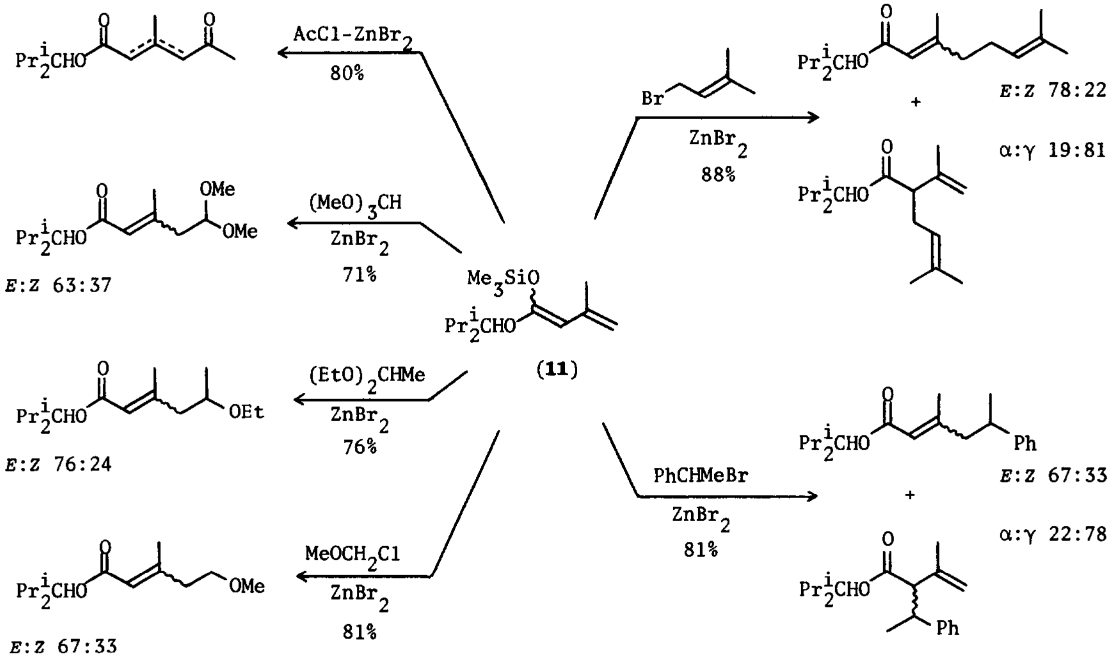
The α:γ ratios obtained were dependent upon the substitution pattern of the diene, the steric size of the alkoxy group (for esters), and the nature of the electrophile. The simple unsubstituted ketone- and ester-derived *O*-silylated dienolates (**6** and **7**) showed very similar selectivities. Introduction of an α-substituent (as in **8**) gave only a small improvement in the γ-selectivity, while a β-substituent (as in **9**) gave a significant increase in regioselectivity in favour of γ-alkylation.[10] The γ-selectivity could be further enhanced, in the case of esters, by using bulky tertiary (Bu^{t}O, as in **10**)[11] or secondary (Pr$^i_2$CHO, as in **11**) alkoxy groups to hinder attack at the α-position. In general, α-chloro-n-butyl phenyl sulphide was more γ-selective than chloromethyl phenyl sulphide.

TABLE: $ZnBr_2$-Catalysed Reactions of *O*-Silylated Dienolates with Phenylthioalkyl Halides

O-Silylated Dienolate		(Yield %)	Electrophile	α:γ[8]	*E*:*Z* for γ	Yield %
(**6**)		(70)	(**4**)	55:45	100:0	65
			(**5**)	34:66	100:0	85
(**7**)		(89)	(**4**)	50:50	100:0	89
			(**5**)	33:67	100:0	84
(**8**)		(93)	(**4**)	44:56	100:0	76
			(**5**)	30:70	100:0	90
(**9**)		(93)	(**4**)	35:65	67:33	97
			(**5**)	16:84	80:20	92
(**10**)		(96)	(**5**)	0:100	74:26	72
(**11**)		(97)	(**4**)	20:80	70:30	91
			(**5**)	0:100	81:19	90
(**12**)			(**5**)	(0:100)[9]	67:33	55
(**13**)		(77)	(**5**)	(0:100)[9]	-	57

As in our earlier work on α-phenylthioalkyl carbonyl compounds,[7] sulphur may be removed both reductively and oxidatively. Desulphurisation of **14** (R = H or Pr^n) and **17** with W-2 Raney nickel[12] (Me_2CO-EtOH, 9:1, 20°, 0.5-2 h) gave the αβ-unsaturated esters (**15**, R = H or Pr^n) and 4-n-butylcyclohexanone (**18**) respectively, representing overall γ-alkylation. Alternatively, oxidative sulphur removal using $NaIO_4$ ($MeOH-H_2O$, 20°, 16 h) followed by heating the sulphoxide (CCl_4, 70°) gave the conjugated diene esters (**16**, R = H, Pr^n) and the dienone (**19**), representing overall γ-alkylidenation.


(**15**) (**14**) (**16**) (**18**) (**17**) (**19**)


(**11**)

Using our most γ-selective *O*-silylated dienolate (**11**), we have also found high γ-selectivity with a range of other carbon electrophiles: acetyl chloride, methyl orthoformate, diethyl acetal, methoxymethyl chloride, α-methyl benzyl bromide and prenyl bromide, all catalysed with zinc bromide.[13]

The *O*-silylated dienolates were prepared from the corresponding αβ- and βγ-unsaturated esters or ketones, as described in the preceding paper. The α-chloroalkyl phenyl sulphides were prepared by chlorination of the corresponding sulphide ($PhSCH_2R$): SO_2Cl_2-CH_2Cl_2 for R = H[14] and NCS for R = Pr^n.[7] For the alkylation reactions, typically, a catalytic amount of powdered anhydrous zinc bromide (*ca*. 10 mg) was added to a solution of the alkylating agent (1.7 mmol) and the *O*-silylated dienolate (1.5 mmol) in dry CH_2Cl_2 (2 ml) at room temperature, and the mixture shaken intermittently. After 5-15 min (for most alkylating agents), 2 h (for $PhSCH_2Cl$), or 16 h (for PhCHMeBr), the solvent was simply evaporated and the residue chromatographed on silica gel to give the alkylated ester or ketone directly. Reductive and oxidative sulphur removal from the α-phenylthioalkyl carbonyl compounds was carried out as described earlier.[7] In the case of the enone (**17**), hydrogenation of the double bond accompanied desulphurisation with Raney nickel to give the saturated ketone (**18**).

NOTES and REFERENCES

[1] Reprints of this paper will not be available.

[2] C. N. Lam, J. M. Mellor, M. F. Rawlins, and J. H. A. Stibbard, *Tetrahedron Letters*, 4103 (1978) and references therein.

[3] J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Letters*, 2433 (1973).

[4] In contrast, condensation reactions with carbonyl electrophiles may be directed to the γ-position under equilibrating conditions, see: I. Casirios and R. Mestres, *J. Chem. Soc. Perkin I*, 1651 (1978) and references therein.

[5] J. A. Katzenellenbogen and A. L. Crumrine, *J. Amer. Chem. Soc.*, **96**, 5662 (1974) and **98**, 4925 (1976); J. A. Oakleaf, M. T. Thomas, A. Wu, and V. Snieckus, *Tetrahedron Letters*, 1645 (1978).

[6] γ-Selective alkylation of lithium dienolates is possible using β-dialkylamino- or γ-phenylsulphonyl-substituted αβ-unsaturated ketones, see: M. Yashimoto, N. Ishisa, and T. Hiraoka, *Tetrahedron Letters*, 39 (1973) and P. T. Lansbury and R. W. Erwin, *ibid.*, 2675 (1978).

[7] I. Paterson and I. Fleming, *Tetrahedron Letters*, 2179 (1979); I. Paterson, *ibid.*, 1519 (1979).

[8] These ratios apply to isolated and recognisable products. Since the yields were not quantitative, the ratios may have been distorted by selective decomposition of one or other product.

[9] No α-product was detected, but the low yields in these cases make these figures unreliable.

[10] A β-siloxy group has also been found to increase γ-selectivity: P. Brownbridge and T. H. Chan, personal communication.

[11] The Pr$_2^i$CH group was superior to Bu^t, because the $ZnBr_2$ also catalysed the removal of the latter group, giving the carboxylic acid as well as ester products.

[12] R. Mozingo, *Org. Synth.*, Coll Vol. III, 181 (1955).

[13] Mukaiyama and Ishida had shown[15] that the *O*-silylated dienolate of crotonaldehyde and of 2,2-dimethylacrolein (**12**) gave γ-alkylation with acetals in the presence of $TiCl_4$-Ti(Pr^{i}O)$_4$. Our observation that the *O*-silylated dienolates (**6**), (**7**), and (**9**) give easily measurable amounts of α-alkylation would seem to indicate that a phenyl or electron-donating substituent at C-1 increases reactivity at the α-position (C-2) somewhat more that at the γ-position (C-4). Comparison, however, is not straightforward as yet, since we are using different electrophiles, and our one reaction with **12**, although we could not find any α-product, did not give a high yield.

[14] B. M. Trost and R. A. Kunz, *J. Org. Chem.*, **39**, 2648 (1974).

[15] T. Mukaiyama and A. Ishida, *Chemistry Letters*, 319 and 1201 (1975) and 467 (1977).

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